Amendments to the Drawings:

The attached replacement sheets of drawings includes changes to Figure 1 and Figure 2, and replace the original sheets including Figures 1 and 2.

Attachments following last page of this Amendment:

Replacement Sheet (2 pages)
Annotated Sheet Showing Change(s) (2 pages)

REMARKS

Following entry of the above amendment, claims 28-30 and 41-48 will be pending in this application, claims 28-30 having been amended and new claims 41-48 added. Support for the amendments to claims 28-30 can be found throughout the specification and claims as originally filed, e.g., at page 4, line 32 to page 5, line 8; page 6, lines 8-12; page 19, lines 22-29; and page 22, lines 1-8. Support for the new claims can be found throughout the specification and claims as originally filed, for example at page 4, line 32, to page 5, line 5; page 9, lines 26-33; page 28, lines 4-23; and Figure 2. No new matter has been added.

Specification

The Office Action requested that the specification at page 1, line 4, be amended to reflect the status of the parent 09/855,266 application. The paragraph has been amended to reflect that application 09/855,266 has issued as U.S. Patent No. 6,784,284.

Applicants have also amended the title of the application to read "ISOLATED ANTIBODIES TO A SECRETORY MEMBRANE PROTEIN", which Applicants believe is indicative of the claims in this application.

The amendments to the drawings append sequence identifiers to Figures 1 and 2, including the sequence identifier for SEQ ID NO:14. The amended sequence listing incorporates sequence information for SEQ ID NO:14 from Figure 2, and thus was prepared from sequences contained in the specification as filed and does not include new matter.

Rejection under 35 USC § 101

Claims 28-30 were rejected under § 101 for allegedly being directed to non-statutory subject matter. In accordance with the Examiner's helpful suggestion at the top of page 3 of the Office Action, Applicants have limited the antibodies of the claims to "isolated" antibodies. As indicated by the Examiner, this limitation clearly distinguishes the claimed antibodies from those that occur naturally (assuming any antibodies meeting the other criteria of the claim indeed exist

naturally, a situation that Applicants doubt is true). Accordingly, Applicants request reconsideration and withdrawal of the rejection.

Rejection under 35 USC § 112, second paragraph

Claim 30 was rejected under § 112, second paragraph, as allegedly being indefinite. Claim 30 is drawn to antibodies that specifically bind to a polypeptide encoded by a first nucleic acid that hybridizes under defined conditions to a second nucleic consisting of a defined part of the antisense strand of SEQ ID NO:3, wherein the first nucleic acid encodes a polypeptide with a defined activity. SEQ ID NO:3 is a representation not only of the sense strand, but also inherently its corresponding antisense strand as well. This interpretation is clear, e.g., from claim 22 of U.S. Patent No. 6,784,284, the parent of the present application, which relies on the same disclosure as the present application. It is fully consistent with the U.S. Patent and Trademark Office's rules regarding sequence listings for nucleic acids, which do not require that double-stranded DNAs be represented by two separate listings (one for each strand), or by a listing that explicitly shows both sense and antisense strands together. Applicants have explicitly limited present claim 30 to hybridization to the antisense strand of SEQ ID NO:3, to satisfy the Examiner's concern, but it is believed that the claim was adequately definite even without that change.

Rejections under 35 USC § 112, first paragraph

Claims 28 and 30 were rejected under §112, first paragraph, as allegedly not enabled for any antibody that binds to a polypeptide that can induce differentiation of an osteocyte, wherein 1) the polypeptide has an amino acid sequence 60% identical to SEQ ID NO:2 or 2) the polypeptide is encoded by a nucleic acid that hybridizes under stringent conditions to a nucleic acid consisting of SEQ ID NO:3. The Office Action alleges that undue experimentation would be required to practice the claimed invention, citing the scope of the claims, the amount of direction or guidance provided, the working examples, the predictability of the art, and the amount of experimentation required to enable one of skill in the art to practice the invention. To

the extent the rejection may be applied to any of the claims as presently amended, Applicants respectfully traverse.

Applicants have amended claim 28 to recite that the polypeptide to which the antibody binds has a sequence 90% identical to SEQ ID NO:2 and have amended claim 30 to recite the hybridization conditions and the region of SEQ ID NO:3 to which hybridization takes place. Applicants have also added new claims 41-48. These amended and new claims are analogous to those granted in U.S. Patent No. 6,784,284, the parent of this divisional application. Applicants maintain that the amended and new claims comply with the enablement requirements of § 112, first paragraph.

Applicants provide ample guidance regarding the structure and function of the 7F4 protein (SEQ ID NO:1 and 2) and the changes and modification that can be made to the protein while retaining function. For example, Applicants identify the 7F4 protein as a member of the TNF receptor (TNFR) superfamily, a well-characterized group of type 1-membrane proteins containing characteristic cysteine-rich repeats in the extracellular domain (page 6, lines 21-31 and page 27, lines 10-15). The identity and location of conserved residues and divergent residues between 7F4 protein and mouse TNF receptor are shown in Figure 2. Further structural comparison of the 7F4 protein to other members of the TNFR superfamily is provided in Figure 6. An ordinary skilled artisan could readily use this information, coupled with the knowledge in the art, to determine what residues of the polypeptides can tolerate changes while still retaining the ability to induce osteocyte differentiation. For example, an ordinary skilled artisan would predict that the cysteine rich repeats and other conserved residues shown in Figures 1 and 2 are important for biological activity. In addition, Example 8 provides a routine assay for determining whether a polypeptide induces osteocyte differentiation utilizing KUSA osteoblast cells. The assay involves transfection of KUSA cells with a polypeptide. Transfection with a polypeptide of the invention causes differentiation of the KUSA cells. Such an assay can be performed by routine methods in a high throughput format.

A balancing of the Wands factors in the present case supports enablement. The claims, as presently amended, are narrow, being directed to polypeptides having a very high degree of

structural similarity to the reference sequence and a specific, readily assayable biological activity. The knowledge and skill in the art for producing the claimed polypeptides is high. The specification provides a working example and substantial guidance on how to identify polypeptides that have the recited activity. With regard to the quantity of experimentation needed, MPEP §2164.01 provides that "the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." Similarly, the fact that some time and expense may be required does not necessarily make the experimentation undue. In *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989) (see also MPEP §2164.06), the requirement of approximately $50,000 and 6-12 months of experimentation was not undue experimentation where the application disclosed one embodiment and a method to determine other embodiments, similar to the instant case. In the present case, making and testing the claimed polypeptides would employ only molecular and cell biology techniques disclosed in the specification and routinely practiced in the art.

With regard to the level of predictability in the art, Applicants submit that the situation is not as dire as the Examiner suggests. Indeed, while it is surely true that in some instances a modification, such as a conservative substitution, can affect the function of a polypeptide, it also recognized in the art that, for any given protein, many residues can be substituted without affecting the protein's function. Bowie et al. (1990) "Deciphering the message in protein sequences: tolerance to amino acid substitutions," Science 247:1306-1310 (copy enclosed as Exhibit A) teaches that "proteins are surprisingly tolerant of amino acid substitutions". Bowie cites as evidence a study carried out on the *lac* repressor. Of approximately 1500 single amino acid substitutions at 142 positions in this protein, about one-half of the substitutions were found to be "phenotypically silent": that is, had no noticeable effect on the activity of the protein (Bowie at page 1306, col. 2, lines 14-17). Presumably the other half of the substitutions exhibited effects ranging from slight to complete abolishment of repressor activity. Thus, one can expect, based on the teachings of Bowie et al., to find over half (and possibly well over half) of random substitutions in any given protein to result in proteins with full or nearly full activity.

Where, as here, one would know to avoid certain types of substitutions in conserved regions, the chances of accidentally abolishing activity with a given substitution is even lower than in the random study described by Bowie et al.

Based at least on the teachings of Bowie et al., the Examiner's assertion that "the skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO:2 to share the same function as the polypeptide of SEQ ID NO:2" (page 5) is wholly without merit. Applicants further note that the majority of the references cited in the Office Action do not relate to the functional activity of protein variants, but rather to the capacity of those variants to bind to antibodies raised against the original protein. Where the cited references do relate to the functional activity of the protein variants, they tend to concur with Bowie et al. in support of Applicants' position. For example, Abaza et al. disclose seven proteins that differ from sperm whale myoglobin at from 15 to 41 amino acid residues (Tables IV-VI), yet are all functional myoglobin proteins. Lederman et al. teach that individuals with a CD4 that does not bind to the monoclonal antibody OKT4 "appear to have grossly normal immune functions and are not immunosuppressed" (p. 1172, col. 1). Metzler et al. disclose that four out of nine mutations of CTLA-4 in regions of the protein predicted by the crystal structure to be important for ligand binding had, in fact, very little effect on binding (Table 2). Li et al. teach that seven out of eleven single amino acid deletion mutants of β-endorphin "gave substantial retention of opiate potencies" (abstract).

Applicants respectfully point out that the claims do not require that the claimed antibodies must be able to bind to SEQ ID NO:2 as well as to the polypeptide that was used as the immunogen. Rather, the claimed antibody need only bind to any one of the polypeptides described in the claim in order to meet the criteria of the claim. Such an antibody clearly meets the enablement requirement, because one of ordinary skill would know perfectly well how to make and use it: simply immunize an animal with an immunogen that is the polypeptide having the specified degree of identity (90% or whatever) to SEQ ID NO:2, or the polypeptide encoded by the nucleic acid that hybridizes to SEQ ID NO:3 under stringent conditions, using standard

methods; purify the antibody by standard means; and use the antibody for isolating or assaying the same polypeptide as that used to raise the antibody.

Moreover, Applicants note that the Examiner's argument seems to be focusing on the "unpredictability" factor of Wands to the exclusion of the other factors. Wands requires a balancing of all the factors. On balance, given the specific limitations recited in the claims, the high level of skill in the art, the detailed guidance provided by Applicants, the disclosure of a working example, and the routine nature of any experimentation that might be required to make and use the polypeptides to which the claimed antibodies bind, the present claims are clearly enabled.

The Office Action has also rejected claim 30 for alleged lack of enablement, stating that:

> Nucleic acid hybridization is a process by which the DNA of a gene is detected by its base pairing with a complementary (antisense) sequence on another nucleic acid molecule. One cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to an antibody that specifically binds to the polypeptide that is encoded by a complementary (antisense) sequence of a nucleic acid. Said antisense sequence does not encode the 7F4 polypeptide of SEQ ID NO:2 and thus polypeptide [*sic*] encoded by antisense sequence can not induces [*sic*] differentiation of an osteocyte.

As discussed above, claim 30 has been amended to make explicit the understanding that the hybridization is to the antisense strand of SEQ ID NO:3, thereby allaying the Examiner's concerns in that regard.

The Office Action has further rejected claim 30 for alleged lack of enablement, stating that:

> hybridization language in the absence of limitations regarding the sequence length over which the hybridization takes place; does not allow the skilled artisan to make and use any antibody that specifically binds to a polypeptide encoded by the first nucleic acid that hybridized under stringent conditions to a second nucleic acid consisting of SEQ ID NO:3.

Applicants respectfully traverse, as undue experimentation would not be required for one of skill in the art to make and use the antibody of claim 30. A person of skill in the art could simply identify nucleic acids that hybridize to SEQ ID NO:3 under the specified conditions (e.g., as described in Example 2), produce the polypeptides encoded by those nucleic acids (e.g., as

described in Examples 4 and 6), and test those polypeptides for the ability to induce differentiation of an osteocyte (e.g., as described in Example 8). As discussed above, making and testing the polypeptides of claim 30 would employ only molecular and cell biology techniques disclosed in the specification and routinely practiced in the art. In the context of the functional language of claim 30, a recitation of the length of hybridization is not necessary.

Claims 28 and 30 were also rejected for allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

To begin, Applicants have amended claim 28 to increase the required degree of structural identity to 90%, substantially narrowing the scope of the claim. The rejection is respectfully traversed insofar as it may be applied to the present claims. The polypeptides to which the claimed antibodies bind are limited structurally in that they have extremely high (at least 90%) sequence identity to a specific reference sequence (claim 28), have a very limited number of conservative substitutions compared to the reference sequence (claims 43-46), or are encoded by a DNA that hybridizes under specific stringent conditions to the reference sequence (claim 30). The polypeptides are also quite limited functionally in that they have a specific (and readily assayable) biological activity, namely induction of osteocyte differentiation. The specific structural and functional limitations of the claims substantially limit the variation within the genus of the polypeptides to which the claimed antibodies bind.

With regard to claim 30 in particular, the Examiner is directed to Example 9 of the Written Description Guidelines Training Materials (the Training Materials), which indicates that claims of a scope comparable to the present claims meet the written description requirement, even though supported by a disclosure containing far less detail than the present one. In particular, Example 9 of the Training Materials concludes that:

> a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

Example 9 concludes that written description is adequate even though the specification discloses only a single species that falls within the claims. A similar conclusion is reached in Example 14 of the Training Materials, where the claimed polypeptide is defined by its high percent of identity to a single disclosed reference sequence, combined with a biological function (as is the case with present claims 28, and 41-46). The Examiner is reminded that the Federal Circuit, in *Enzo Biochem, Inc. v. Gen-Probe Inc.* (296 F.3d 1316, Fed. Cir. 2002), has taken judicial notice of the Written Description Guidelines and the Training Materials, and found them persuasive. Accordingly, under the PTO's own Guidelines and Training Materials, and under Federal Circuit law, the claims meet the written description requirement.

The Office Action further cites *Fiers v. Revel*, 984 F. 2d 1169, 25 USPQ2d 1601 (1993), as support for rejection of the present claims, stating that:

> A description of what the material does i.e. antibody [*sic*] that bind to a polypeptide, wherein said polypeptide induces differentiation of an osteocyte, rather than what it is, usually does not suffice.

Applicants point out that *Fiers* is not applicable here. In *Fiers*, the issue was a disclosure that did not contain any structural description of the claimed DNA or the polypeptides encoded thereby. In contrast, here the polypeptides to which the presently claimed antibodies bind are clearly described in structural as well as functional terms sufficient to meet the written description requirement; indeed, claims drawn to these polypeptides were granted in the parent patent. Given that fact, antibodies that bind to those fully described polypeptides also meet the written description requirement under U.S. law. The Federal Circuit's decision in *Noelle v. Lederman*, 355 F.3d 1343, 69 USPQ2d 1508 (Fed. Cir. 2004), makes that clear. The *Noelle* court held that:

> [A]s long as an applicant has disclosed a "fully characterized antigen," either by its structure, formula, chemical name, or physical properties, or by depositing the protein in a public depository, the applicant can then claim an antibody by its binding affinity to that described antigen.

Applicants submit that the antigens recited in the claims, e.g.,

a polypeptide, the amino acid sequence consists of a sequence at least 90% identical to SEQ ID NO: 2, wherein the polypeptide induces differentiation of an osteocyte (claim 28);

a polypeptide encoded by a first nucleic acid that hybridizes under stringent conditions (0.2 X SSC and 0.1% SDS at 68 °C) to a second nucleic acid consisting of the antisense strand of the coding region of SEQ ID NO: 3, wherein the polypeptide induces differentiation of an osteocyte (claim 30);

a polypeptide, the amino acid sequence of which consists of SEQ ID NO: 2 containing up to 30 conservative amino acid substitutions, wherein the polypeptide induces differentiation of an osteoblast (claim 43); and

the extracellular region of 7F4 (SEQ ID NO: 14) (claim 47),

are fully characterized antigens meeting both the written description and enablement requirements, for at least the reasons discussed above and as evidenced by the grant of a patent directed to polypeptides of similar or broader scope. Therefore, based on the reasoning of *Noelle*, the present claims are both sufficiently described and fully enabled.

Applicants respectfully submit that the present claims are in condition for allowance and request confirmation of such from the Examiner. Enclosed is Petition for Extension of Time along with the required fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 14875-040003.

Respectfully submitted,

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